09/693,558

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PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

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NEWS 1		Web Page for STN Seminar Schedule - N. America
NEWS 2	MAY 01	New CAS web site launched
NEWS 3	MAY 08	CA/CAplus Indian patent publication number format defined
NEWS 4	MAY 14	RDISCLOSURE on STN Easy enhanced with new search and display fields
NEWS 5	MAY 21	BIOSIS reloaded and enhanced with archival data
NEWS 6	MAY 21	TOXCENTER enhanced with BIOSIS reload
NEWS 7	MAY 21	CA/CAplus enhanced with additional kind codes for German patents
NEWS 8	MAY 22	CA/CAplus enhanced with IPC reclassification in Japanese patents
NEWS 9	JUN 27	CA/CAplus enhanced with pre-1967 CAS Registry Numbers
NEWS 10	JUN 29	STN Viewer now available
NEWS 11	JUN 29	STN Express, Version 8.2, now available
NEWS 12	JUL 02	LEMBASE coverage updated
NEWS 13	JUL 02	LMEDLINE coverage updated
NEWS 14	JUL 02	SCISEARCH enhanced with complete author names
NEWS 15	JUL 02	CHEMCATS accession numbers revised
NEWS 16	JUL 02	CA/CAplus enhanced with utility model patents from China
NEWS 17	JUL 16	CAplus enhanced with French and German abstracts
NEWS 18	JUL 18	CA/CAplus patent coverage enhanced
NEWS 19	JUL 26	USPATFULL/USPAT2 enhanced with IPC reclassification
NEWS 20	JUL 30	USGENE now available on STN
NEWS 21	AUG 06	CAS REGISTRY enhanced with new experimental property tags
NEWS 22	AUG 06	BEILSTEIN updated with new compounds
NEWS 23	AUG 06	FSTA enhanced with new thesaurus edition

NEWS EXPRESS 29 JUNE 2007: CURRENT WINDOWS VERSION IS V8.2,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 05 JULY 2007.

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8

Enter NEWS followed by the item number or name to see news on that specific topic.

* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 16:30:00 ON 09 AUG 2007

=> file registry

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 16:30:18 ON 09 AUG 2007

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 8 AUG 2007 HIGHEST RN 944313-22-8
DICTIONARY FILE UPDATES: 8 AUG 2007 HIGHEST RN 944313-22-8

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TSCA INFORMATION NOW CURRENT THROUGH December 2, 2006

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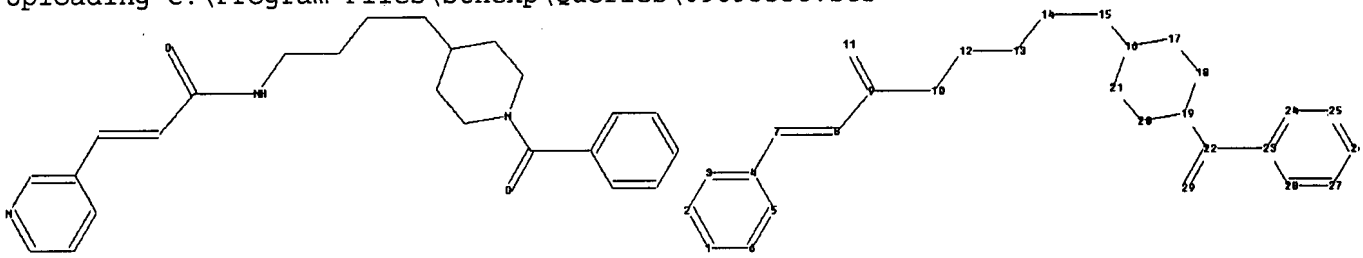
REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=>
Uploading C:\Program Files\Stnexp\Queries\09693558.str



chain nodes :
7 8 9 10 11 12 13 14 15 22 29
ring nodes :
1 2 3 4 5 6 16 17 18 19 20 21 23 24 25 26 27 28
chain bonds :
4-7 7-8 8-9 9-10 9-11 10-12 12-13 13-14 14-15 15-16 19-22 22-23 22-29

ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 16-17 16-21 17-18 18-19 19-20 20-21 23-24 23-28
24-25 25-26 26-27 27-28
exact/norm bonds :
9-10 9-11 10-12 16-17 16-21 17-18 18-19 19-20 19-22 20-21 22-29

exact bonds :
4-7 7-8 8-9 12-13 13-14 14-15 15-16 22-23
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 23-24 23-28 24-25 25-26 26-27 27-28

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 9:CLASS 10:CLASS
11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:Atom 17:Atom 18:Atom
19:Atom 20:Atom
21:Atom 22:CLASS 23:Atom 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom 29:CLASS

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

Structure attributes must be viewed using STN Express query preparation.

=> s l1 exa full
FULL SEARCH INITIATED 16:30:53 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 4 TO ITERATE

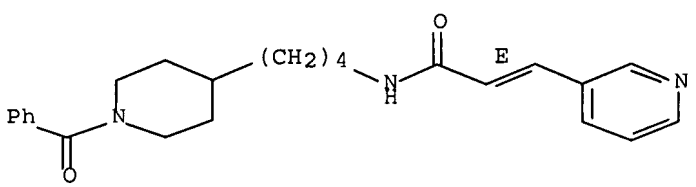
100.0% PROCESSED 4 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.01

L2 2 SEA EXA FUL L1

=> d l2 1-2

L2 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2007 ACS on STN
RN 658084-64-1 REGISTRY
ED Entered STN: 04 Mar 2004
CN 2-Propenamide, N-[4-(1-benzoyl-4-piperidinyl)butyl]-3-(3-pyridinyl)-,
(2E)- (CA INDEX NAME)
OTHER NAMES:
CN FK 866
CN K 22.175
FS STEREOSEARCH
MF C24 H29 N3 O2
SR CA
LC STN Files: CA, CAPLUS, IMSDRUGNEWS, IMSRESEARCH, PROUSDDR, TOXCENTER

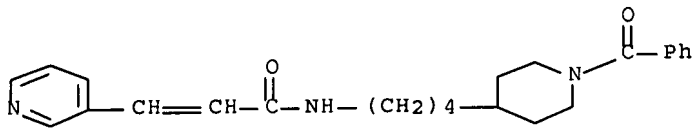
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

7 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
7 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2007 ACS on STN
RN 201034-75-5 REGISTRY
ED Entered STN: 10 Feb 1998
CN 2-Propenamide, N-[4-(1-benzoyl-4-piperidinyl)butyl]-3-(3-pyridinyl)- (9CI) (CA INDEX NAME)
MF C24 H29 N3 O2
SR CA
LC STN Files: ADISINSIGHT, CA, CAPLUS, PROUSDDR, TOXCENTER, USPAT2, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file medline caplus wpids uspatfull

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	62.60	62.81

FILE 'MEDLINE' ENTERED AT 16:31:20 ON 09 AUG 2007

FILE 'CAPLUS' ENTERED AT 16:31:20 ON 09 AUG 2007
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE 'WPIDS' ENTERED AT 16:31:20 ON 09 AUG 2007
COPYRIGHT (C) 2007 THE THOMSON CORPORATION

FILE 'USPATFULL' ENTERED AT 16:31:20 ON 09 AUG 2007
CA INDEXING COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

=> s l2
SAMPLE SEARCH INITIATED 16:31:26 FILE 'WPIDS'
SAMPLE SCREEN SEARCH COMPLETED - 0 TO ITERATE

100.0% PROCESSED 0 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 0 TO 0
PROJECTED ANSWERS: 0 TO 0

L3 17 L2

=> s l17 and nicotinamide
L17 NOT FOUND
The L-number entered could not be found. To see the definition of L-numbers, enter DISPLAY HISTORY at an arrow prompt (=>).

=> s l3 and nicotinamide
L4 6 L3 AND NICOTINAMIDE

=> d l4 1-6 ibib, abs, hit

L4 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1215147 CAPLUS Full-text
DOCUMENT NUMBER: 146:155520
TITLE: Chemopotentiating effects of a novel NAD biosynthesis inhibitor, FK866, in combination with antineoplastic agents
AUTHOR(S): Pogrebniak, A.; Schemainda, I.; Azzam, K.; Pelka-Fleischer, R.; Nuessler, V.; Hasmann, M.
CORPORATE SOURCE: Department of Pathology, University of Ulm, Germany
SOURCE: European Journal of Medical Research (2006), 11(8), 313-321
CODEN: EJMRFL; ISSN: 0949-2321
PUBLISHER: I. Holzapfel Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English

AB FK866 is a novel anticancer agent that was previously shown to interfere with NAD+ biosynthesis by inhibition of nicotinamide phosphoribosyltransferase and to initiate apoptosis in cancer cells. As NAD+ is involved in cellular DNA repair processes, the present in vitro study on THP-1 and K562 leukemia cells was conducted to investigate the cytotoxicity of FK866 combination treatment with various cytotoxic agents: the antimetabolite Ara-C, the DNA-intercalating agent daunorubicin and the alkylating compds. 1-methyl-3-nitro-1-nitrosoguanidinium (MNNG) and melphalan. Cell viability after drug exposure was assessed by propidium iodide (PI) staining. Non-cytotoxic concns. of FK866 (10-9M or less), applied simultaneously or 24 h before adding cytotoxic agents, caused a depletion in the intracellular NAD+ and - to a lesser extent - NADH levels in THP-1 cells. After 48 and 72 h treatment with daunorubicin and Ara-C, resp., increased cell death was observed in THP-1 cells that were pretreated with FK866, as compared to cells exposed to antineoplastic drugs alone. However, this effect was transient, and there was no difference in cell survival after 72 h incubation with daunorubicin or 96 h with Ara-C. Non-toxic concns. of FK866 added 8, 16, or 24 h before starting treatment with the PARP-activating agent MNNG synergistically decreased intracellular NAD+ contents, and increased MNNG-induced cytotoxicity both in THP-1 and K562 cells for at least 72 h. This effect was less pronounced when FK866 was used in combination with another alkylating agent, melphalan. The PARP inhibitor 3-aminobenzamide delayed MNNG-induced cytotoxicity by 24 h both in cells that were pretreated with FK866 and in non-pretreated cells. 48 H later, the protective effect of 3-aminobenzamide could no longer be observed, but FK866-pretreated cells retained increased sensitivity to MNNG. In conclusion, the chemosensitizing effect of FK866 on cell death induced by antineoplastic drugs was particularly obvious in combination with substances like MNNG that cause NAD+ depletion per se. It was less pronounced and only transiently measurable

in combination with daunorubicin, Ara-C, and melphalan, resp. These results may indicate different levels of DNA damage implicated in the action of the cytotoxic agents used.

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB FK866 is a novel anticancer agent that was previously shown to interfere with NAD+ biosynthesis by inhibition of nicotinamide phosphoribosyltransferase and to initiate apoptosis in cancer cells. As NAD+ is involved in cellular DNA repair processes, the present in vitro study on THP-1 and K562 leukemia cells was conducted to investigate the cytotoxicity of FK866 combination treatment with various cytotoxic agents: the antimetabolite Ara-C, the DNA-intercalating agent daunorubicin and the alkylating compds. 1-methyl-3-nitro-1-nitrosoguanidinium (MNNG) and melphalan. Cell viability after drug exposure was assessed by propidium iodide (PI) staining. Non-cytotoxic concns. of FK866 (10-9M or less), applied simultaneously or 24 h before adding cytotoxic agents, caused a depletion in the intracellular NAD+ and - to a lesser extent - NADH levels in THP-1 cells. After 48 and 72 h treatment with daunorubicin and Ara-C, resp., increased cell death was observed in THP-1 cells that were pretreated with FK866, as compared to cells exposed to antineoplastic drugs alone. However, this effect was transient, and there was no difference in cell survival after 72 h incubation with daunorubicin or 96 h with Ara-C. Non-toxic concns. of FK866 added 8, 16, or 24 h before starting treatment with the PARP-activating agent MNNG synergistically decreased intracellular NAD+ contents, and increased MNNG-induced cytotoxicity both in THP-1 and K562 cells for at least 72 h. This effect was less pronounced when FK866 was used in combination with another alkylating agent, melphalan. The PARP inhibitor 3-aminobenzamide delayed MNNG-induced cytotoxicity by 24 h both in cells that were pretreated with FK866 and in non-pretreated cells. 48 H later, the protective effect of 3-aminobenzamide could no longer be observed, but FK866-pretreated cells retained increased sensitivity to MNNG. In conclusion, the chemosensitizing effect of FK866 on cell death induced by antineoplastic drugs was particularly obvious in combination with substances like MNNG that cause NAD+ depletion per se. It was less pronounced and only transiently measurable in combination with daunorubicin, Ara-C, and melphalan, resp. These results may indicate different levels of DNA damage implicated in the action of the cytotoxic agents used.

IT 58-68-4, NADH 147-94-4, Ara-C 148-82-3, Melphalan 20830-81-3, Daunorubicin 658084-64-1, FK866
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chemopotentiating effects of a novel NAD biosynthesis inhibitor, FK866, in combination with antineoplastic agents)

L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:880871 CAPLUS Full-text
DOCUMENT NUMBER: 145:413038
TITLE: Crystal structure of visfatin/pre-B cell colony-enhancing factor 1/nicotinamide phosphoribosyltransferase, free and in complex with the anti-cancer agent FK-866
AUTHOR(S): Kim, Mun-Kyoung; Lee, Jun Hyuck; Kim, Hun; Park, Soo Jeong; Kim, Sung Hyun; Kang, Gil Bu; Lee, Yun Sok; Kim, Jae Bum; Kim, Kyeong Kyu; Suh, Se Won; Eom, Soo Hyun
CORPORATE SOURCE: Department of Life Science, Gwangju Institute of Science & Technology, Gwangju, 500-712, S. Korea
SOURCE: Journal of Molecular Biology (2006), 362(1), 66-77
CODEN: JMOBAK; ISSN: 0022-2836
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Visfatin/pre-B cell colony-enhancing factor 1 (PBEF)/nicotinamide phosphoribosyltransferase (NAmPRTase) is a multifunctional protein having phosphoribosyltransferase, cytokine and adipokine activities. Originally isolated as a cytokine promoting the differentiation of B cell precursors, it was recently suggested to act as an insulin analog via the insulin receptor. Here, we describe the first crystal structure of visfatin in three different forms: apo and in complex with either NMN or the NAmPRTase inhibitor FK-866 which was developed as an anti-cancer agent, interferes with NAD biosynthesis, showing a particularly high specificity for NAmPRTase. The crystal structures of the complexes with either NMN or FK-866 show that the enzymic active site of visfatin is optimized for nicotinamide binding and that the nicotinamide-binding site is important for inhibition by FK-866. Interestingly, visfatin mimics insulin signaling by binding to the insulin receptor with an affinity similar to that of insulin and does not share the binding site with insulin on the insulin receptor. To predict binding sites, the potential interaction patches of visfatin and the L1-CR-L2 domain of insulin receptor were generated and analyzed. Although the relationship between the insulin-mimetic property and the enzymic function of visfatin has not been clearly established, our structures raise the intriguing possibility that the glucose metabolism and the NAD biosynthesis are linked by visfatin.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Crystal structure of visfatin/pre-B cell colony-enhancing factor 1/ nicotinamide phosphoribosyltransferase, free and in complex with the anti-cancer agent FK-866

AB Visfatin/pre-B cell colony-enhancing factor 1 (PBEF)/nicotinamide phosphoribosyltransferase (NAmPRTase) is a multifunctional protein having phosphoribosyltransferase, cytokine and adipokine activities. Originally isolated as a cytokine promoting the differentiation of B cell precursors, it was recently suggested to act as an insulin analog via the insulin receptor. Here, we describe the first crystal structure of visfatin in three different forms: apo and in complex with either NMN or the NAmPRTase inhibitor FK-866 which was developed as an anti-cancer agent, interferes with NAD biosynthesis, showing a particularly high specificity for NAmPRTase. The crystal structures of the complexes with either NMN or FK-866 show that the enzymic active site of visfatin is optimized for nicotinamide binding and that the nicotinamide-binding site is important for inhibition by FK-866. Interestingly, visfatin mimics insulin signaling by binding to the insulin receptor with an affinity similar to that of insulin and does not share the binding site with insulin on the insulin receptor. To predict binding sites, the potential interaction patches of visfatin and the L1-CR-L2 domain of insulin receptor were generated and analyzed. Although the relationship between the insulin-mimetic property and the enzymic function of visfatin has not been clearly established, our structures raise the intriguing possibility that the glucose metabolism and the NAD biosynthesis are linked by visfatin.

ST crystal structure visfatin nicotinamide phosphoribosyltransferase complex FK866 NMN; pre B cell colony enhancing factor 1 insulin receptor

IT Insulin receptors
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(FK-866 and NMN bind at dimeric interface of visfatin/pre-B cell colony-enhancing factor 1/nicotinamide phosphoribosyltransferase)

IT Enzyme functional sites
(active; FK-866 and NMN bind at dimeric interface of visfatin/pre-B cell colony-enhancing factor 1/nicotinamide phosphoribosyltransferase)

IT Crystal structure

(of visfatin/pre-B cell colony-enhancing factor 1/nicotinamide phosphoribosyltransferase, free and in complex with FK-866 and NMN)

IT 9030-27-7, Proteins, pre-B cell colony-enhancing factor
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(1, complexes with NMN and FK-866; FK-866 and NMN bind at dimeric interface of visfatin/pre-B cell colony-enhancing factor 1/nicotinamide phosphoribosyltransferase)

IT 53-84-9, NAD
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(FK-866 and NMN bind at dimeric interface of visfatin/pre-B cell colony-enhancing factor 1/nicotinamide phosphoribosyltransferase)

IT 1094-61-7D, NMN, complexes with nicotinamide phosphoribosyltransferase 658084-64-1D, FK 866, complexes with nicotinamide phosphoribosyltransferase
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(FK-866 and NMN bind at dimeric interface of visfatin/pre-B cell colony-enhancing factor 1/nicotinamide phosphoribosyltransferase)

IT 9030-27-7D, Nicotinamide phosphoribosyltransferase, complexes with FK-866
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(visfatin; FK-866 and NMN bind at dimeric interface of visfatin/pre-B cell colony-enhancing factor 1/nicotinamide phosphoribosyltransferase)

L4 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:663657 CAPLUS Full-text
DOCUMENT NUMBER: 145:202228
TITLE: Molecular basis for the inhibition of human NMPRTase, a novel target for anticancer agents
AUTHOR(S): Khan, Javed A.; Tao, Xiao; Tong, Liang
CORPORATE SOURCE: Department of Biological Sciences, Columbia University, New York, NY, 10027, USA
SOURCE: Nature Structural & Molecular Biology (2006), 13(7), 582-588
CODEN: NSMBCU; ISSN: 1545-9993
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Nicotinamide phosphoribosyltransferase (NMPRTase) has a crucial role in the salvage pathway of NAD+ biosynthesis, and a potent inhibitor of NMPRTase, FK866, can reduce cellular NAD+ levels and induce apoptosis in tumors. The authors have determined the crystal structures at up to 2.1-Å resolution of human and murine NMPRTase, alone and in complex with the reaction product NMN or the inhibitor FK866. The structures suggest that Asp219 is a determinant of substrate specificity of NMPRTase, which is confirmed by our mutagenesis studies. FK866 is bound in a tunnel at the interface of the NMPRTase dimer, and mutations in this binding site can abolish the inhibition by FK866. Contrary to current knowledge, the structures show that FK866 should compete directly with the nicotinamide substrate. Our structural and biochem. studies provide a starting point for the development of new anticancer agents.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Nicotinamide phosphoribosyltransferase (NMPRTase) has a crucial role in the salvage pathway of NAD+ biosynthesis, and a potent inhibitor of NMPRTase, FK866, can reduce cellular NAD+ levels and induce apoptosis in tumors. The

authors have determined the crystal structures at up to 2.1-Å resolution of human and murine NMPRTase, alone and in complex with the reaction product NMN or the inhibitor FK866. The structures suggest that Asp219 is a determinant of substrate specificity of NMPRTase, which is confirmed by our mutagenesis studies. FK866 is bound in a tunnel at the interface of the NMPRTase dimer, and mutations in this binding site can abolish the inhibition by FK866. Contrary to current knowledge, the structures show that FK866 should compete directly with the nicotinamide substrate. Our structural and biochem. studies provide a starting point for the development of new anticancer agents.

IT Crystal structure
(of nicotinamide phosphoribosyltransferase)

IT 9030-27-7, Nicotinamide phosphoribosyltransferase
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(mol. basis for inhibition of human NMPRTase, a target for anticancer agents)

IT 658084-64-1, FK 866
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mol. basis for inhibition of human NMPRTase, a target for anticancer agents)

L4 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2003:885670 CAPLUS Full-text
DOCUMENT NUMBER: 140:174633
TITLE: FK866, a Highly Specific Noncompetitive Inhibitor of Nicotinamide Phosphoribosyltransferase, Represents a Novel Mechanism for Induction of Tumor Cell Apoptosis
AUTHOR(S): Hasmann, Max; Schemainda, Isabel
CORPORATE SOURCE: Fujisawa GmbH, Munich, 81673, Germany
SOURCE: Cancer Research (2003), 63(21), 7436-7442
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Deregulation of apoptosis, the physiol. form of cell death, is closely associated with immunol. diseases and cancer. Apoptosis is activated either by death receptor-driven or mitochondrial pathways, both of which may provide potential targets for novel anticancer drugs. Although several ligands stimulating death receptors have been described, the actual mol. events triggering the mitochondrial pathway are largely unknown. Here, we show initiation of apoptosis by gradual depletion of the intracellular coenzyme NAD+. We identified the first low mol. weight compound, designated FK866, which induces apoptosis by highly specific, noncompetitive inhibition of nicotinamide phosphoribosyltransferase (NAPRT), a key enzyme in the regulation of NAD+ biosynthesis from the natural precursor nicotinamide. Interference with this enzyme does not primarily intoxicate cells because the mitochondrial respiratory activity and the NAD+-dependent redox reactions involved remain unaffected as long as NAD+ is not effectively depleted by catabolic reactions. Certain tissues, however, have a high turnover of NAD+ through its cleavage by enzymes like poly(ADP-ribose) polymerase. Such cells often rely on the more readily available nicotinamide pathway for NAD+ synthesis and undergo apoptosis after inhibition of NAPRT, whereas cells effectively using the nicotinic acid pathway for NAD+ synthesis remain unaffected. In support of this concept, FK866 effectively induced delayed cell death by apoptosis in HepG2 human liver carcinoma cells with an IC50 of .apprx.1 nM, did not directly inhibit mitochondrial respiratory activity, but caused gradual NAD+ depletion through specific inhibition of NAPRT. This enzyme, when partially purified from K562 human leukemia cells, was noncompetitively inhibited by

FK866, and the inhibitor consts. were calculated to be 0.4 nM for the enzyme/substrate complex (Ki) and 0.3 nM for the free enzyme (Ki'), resp. Nicotinic acid and nicotinamide were both found to have antidote potential for the cellular effects of FK866. FK866 may be used for treatment of diseases implicating deregulated apoptosis such as cancer for immunosuppression or as a sensitizer for genotoxic agents. Furthermore, it may provide an important tool for investigation of the mol. triggers of the mitochondrial pathway leading to apoptosis through enabling temporal separation of NAD+ decrease from ATP breakdown and apoptosis by several days.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI FK866, a Highly Specific Noncompetitive Inhibitor of Nicotinamide Phosphoribosyltransferase, Represents a Novel Mechanism for Induction of Tumor Cell Apoptosis

AB Deregulation of apoptosis, the physiol. form of cell death, is closely associated with immunol. diseases and cancer. Apoptosis is activated either by death receptor-driven or mitochondrial pathways, both of which may provide potential targets for novel anticancer drugs. Although several ligands stimulating death receptors have been described, the actual mol. events triggering the mitochondrial pathway are largely unknown. Here, we show initiation of apoptosis by gradual depletion of the intracellular coenzyme NAD+. We identified the first low mol. weight compound, designated FK866, which induces apoptosis by highly specific, noncompetitive inhibition of nicotinamide phosphoribosyltransferase (NAPRT), a key enzyme in the regulation of NAD+ biosynthesis from the natural precursor nicotinamide. Interference with this enzyme does not primarily intoxicate cells because the mitochondrial respiratory activity and the NAD+-dependent redox reactions involved remain unaffected as long as NAD+ is not effectively depleted by catabolic reactions. Certain tissues, however, have a high turnover of NAD+ through its cleavage by enzymes like poly(ADP-ribose) polymerase. Such cells often rely on the more readily available nicotinamide pathway for NAD+ synthesis and undergo apoptosis after inhibition of NAPRT, whereas cells effectively using the nicotinic acid pathway for NAD+ synthesis remain unaffected. In support of this concept, FK866 effectively induced delayed cell death by apoptosis in HepG2 human liver carcinoma cells with an IC50 of .apprx.1 nM, did not directly inhibit mitochondrial respiratory activity, but caused gradual NAD+ depletion through specific inhibition of NAPRT. This enzyme, when partially purified from K562 human leukemia cells, was noncompetitively inhibited by FK866, and the inhibitor consts. were calculated to be 0.4 nM for the enzyme/substrate complex (Ki) and 0.3 nM for the free enzyme (Ki'), resp. Nicotinic acid and nicotinamide were both found to have antidote potential for the cellular effects of FK866. FK866 may be used for treatment of diseases implicating deregulated apoptosis such as cancer for immunosuppression or as a sensitizer for genotoxic agents. Furthermore, it may provide an important tool for investigation of the mol. triggers of the mitochondrial pathway leading to apoptosis through enabling temporal separation of NAD+ decrease from ATP breakdown and apoptosis by several days.

ST FK866 nicotinamide phosphoribosyltransferase inhibitor tumor apoptosis

IT Antitumor agents
Apoptosis
Human
(FK866, a highly specific noncompetitive inhibitor of nicotinamide phosphoribosyltransferase, represents a novel mechanism for induction of tumor cell apoptosis)

IT 9030-27-7, Nicotinamide phosphoribosyltransferase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(FK866, a highly specific noncompetitive inhibitor of nicotinamide phosphoribosyltransferase, represents a novel mechanism for induction of tumor cell apoptosis)

IT 658084-64-1, FK 866
RL: PAC (Pharmacological activity); BIOL (Biological study)
(FK866, a highly specific noncompetitive inhibitor of nicotinamide phosphoribosyltransferase, represents a novel mechanism for induction of tumor cell apoptosis)

L4 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:690954 CAPLUS Full-text
DOCUMENT NUMBER: 131:307106
TITLE: Use of vitamin PP compounds as cytoprotective agents in chemotherapy
INVENTOR(S): Biedermann, Elfi; Hasmann, Max; Loser, Roland; Rattel, Benno; Reiter, Friedemann; Schein, Barbara; Schemainda, Isabel; Seibel, Klaus; Vogt, Klaus; Wosikowski, Katja
PATENT ASSIGNEE(S): Klinge Pharma GmbH, Germany
SOURCE: PCT Int. Appl., 145 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9953920	A1	19991028	WO 1999-EP2686	19990421
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW				
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DE 19818044	A1	19991028	DE 1998-19818044	19980422
EP 1031564	A1	20000830	EP 1999-103814	19990226
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AU 9939282	A	19991108	AU 1999-39282	19990421
EP 1079832	A1	20010307	EP 1999-922119	19990421
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JP 2002512190	T	20020423	JP 2000-544324	19990421
AT 311186	T	20051215	AT 1999-922119	19990421
ES 2253890	T3	20060601	ES 1999-922119	19990421
WO 2000050399	A1	20000831	WO 2000-EP1628	20000228
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1154998	A1	20011121	EP 2000-907642	20000228
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JP 2002537380	T	20021105	JP 2000-600982	20000228
EP 1816124	A2	20070808	EP 2007-10337	20000228
R: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				

US 2002160968	A1	20021031	US 2001-935772	20010823
US 6506572	B2	20030114		

PRIORITY APPLN. INFO.:

DE 1998-19818044	A	19980422
EP 1999-103814	A	19990226
WO 1999-EP2686	W	19990421
EP 2000-907642	A3	20000228
WO 2000-EP1628	W	20000228

OTHER SOURCE(S): MARPAT 131:307106

AB The invention relates to the use of vitamin PP compds. and/or compds. with anti-pellagra activity such as for example nicotinic acid (niacin), and nicotinamide (niacin-amide, vitamin PP, vitamin B3) for the reduction, elimination or prevention of side-effects of different degrees as well as for neutralization of acute side-effects in immunosuppressive or cancerostatic chemotherapy or diagnosis, especially with substituted pyridine carboxamides, as well as combination medicaments with an amount of compds. with vitamin B3 and/or anti-pellagra activity and chemotherapeutic agents are especially considered in the mentioned chemotherapies and indications. Nicotinamide at 500 mg/kg twice daily protected mice treated i.p. with antitumor N-[4-(1-diphenylmethylpiperidin-4-yl)butyl]-3-(pyridin-3- yl)propionamide. There were no deaths in the nicotinamide -treated mice and the strong reduction of leukocytes was completely prevented.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB The invention relates to the use of vitamin PP compds. and/or compds. with anti-pellagra activity such as for example nicotinic acid (niacin), and nicotinamide (niacin-amide, vitamin PP, vitamin B3) for the reduction, elimination or prevention of side-effects of different degrees as well as for neutralization of acute side-effects in immunosuppressive or cancerostatic chemotherapy or diagnosis, especially with substituted pyridine carboxamides, as well as combination medicaments with an amount of compds. with vitamin B3 and/or anti-pellagra activity and chemotherapeutic agents are especially considered in the mentioned chemotherapies and indications. Nicotinamide at 500 mg/kg twice daily protected mice treated i.p. with antitumor N-[4-(1-diphenylmethylpiperidin-4-yl)butyl]-3-(pyridin-3- yl)propionamide. There were no deaths in the nicotinamide -treated mice and the strong reduction of leukocytes was completely prevented.

ST vitamin PP cytoprotective agent chemotherapy; side effect redn chemotherapy vitamin PP; antitumor immune system protection nicotinamide; niacin protection immunosuppressive tumor therapy

IT Animal cell line
(THP-1, nicotinic acid and nicotinamide protection of; vitamin PP compds. as cytoprotective agents in chemotherapy)

IT Leukocyte
(antitumor reduction of, in mice, nicotinamide prevention of; vitamin PP compds. as cytoprotective agents in chemotherapy)

IT Intestine
(crypt, nicotinic acid and nicotinamide protection of; vitamin PP compds. as cytoprotective agents in chemotherapy)

IT Lymphocyte
(nicotinic acid and nicotinamide protection of; vitamin PP compds. as cytoprotective agents in chemotherapy)

IT 200867-83-0 201034-75-5
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vitamin PP compds. as cytoprotective agents in chemotherapy)

IT 59-67-6, Nicotinic acid, biological studies 98-92-0, Nicotinamide 11032-50-1, Vitamin PP
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

(Uses)
(vitamin PP compds. as cytoprotective agents in chemotherapy)
IT 59-67-6D, Nicotinic acid, derivs. 98-92-0D, Nicotinamide, derivs.
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vitamin PP compds. as cytoprotective agents in chemotherapy)

L4 ANSWER 6 OF 6 USPATFULL on STN
ACCESSION NUMBER: 2002:288098 USPATFULL Full-text
TITLE: Inhibitors of cellular niacinamide mononucleotide formation and their use in cancer therapy
INVENTOR(S): Biedermann, Elfi, Vaterstetten, GERMANY, FEDERAL REPUBLIC OF
Eisenburger, Rolf, Kirchseeon, GERMANY, FEDERAL REPUBLIC OF
Hasmann, Max, Neuried, GERMANY, FEDERAL REPUBLIC OF
Loser, Roland, Feldafing, GERMANY, FEDERAL REPUBLIC OF
Rattel, Benno, Munich, GERMANY, FEDERAL REPUBLIC OF
Reiter, Friedemann, Putzbrunn, GERMANY, FEDERAL REPUBLIC OF
Schein, Barbara, Neufahrn, GERMANY, FEDERAL REPUBLIC OF
Schemainda, Isabel, Munich, GERMANY, FEDERAL REPUBLIC OF
Schulz, Michael, Aschheim, GERMANY, FEDERAL REPUBLIC OF
Seibel, Klaus, Grafelfing, GERMANY, FEDERAL REPUBLIC OF
Vogt, Klaus, Munich, GERMANY, FEDERAL REPUBLIC OF
Wosikowski, Katja, Poing, GERMANY, FEDERAL REPUBLIC OF
PATENT ASSIGNEE(S): Klinge Pharma GmbH (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002160968	A1	20021031
	US 6506572	B2	20030114
APPLICATION INFO.:	US 2001-935772	A1	20010823 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. WO 2000-EP1628, filed on 28 Feb 2000, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	EP 1999-103814	19990226

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FITCH EVEN TABIN AND FLANNERY, 120 SOUTH LA SALLE STREET, SUITE 1600, CHICAGO, IL, 60603-3406
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 28 Drawing Page(s)
LINE COUNT: 3127
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB New biologically active compounds are described which inhibit the cellular formation of niacinamide mononucleotide, and essential intermediate of the NAD(P) biosynthesis in the cell. These compounds can represent the active ingredient of a pharmaceutical composition for the treatment of cancers, leukaemias or for immunosuppression. Furthermore, screening methods are described as a tool for detecting the above active compounds, and for examination of a given cell type for its dependency on niacinamide as a precursor for NAD synthesis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0004] NAD is synthesized in mammalian cells by three different pathways starting either from tryptophan via quinolinic acid, from niacin (also referred to as nicotinic acid) or from niacinamide (also referred to as nicotinamide), as shown in FIG. 1.

DRWD [0022] FIG. 1: Biochemical Pathways of NAD(P).sup.+ Biosynthesis FIG. 2: Time curve of the action of 6-Amino-nicotinamide in different concentrations on the HepG2 cell growth in comparison to a control and an internal standard determined by the SRB assay.

DRWD [0040] FIG. 20: Influence of nicotinamide on the cell growth inhibition of 6-Amino-nicotinamide at different concentrations.

DRWD [0041] FIG. 21: Influence of nicotinamide on the cell growth inhibition of Tiazofurin at different concentrations.

DRWD [0042] FIG. 22: Influence of nicotinamide on the cell growth inhibition of Selenazofurin at different concentrations.

DRWD [0043] FIG. 23: Influence of nicotinamide on the cell growth inhibition of Azaserin at different concentrations.

DRWD [0044] FIG. 24: Influence of nicotinamide on the cell growth inhibition of 6-Diazo-5-oxo-L-norleucine at different concentrations.

DRWD [0045] FIG. 25: Influence of nicotinamide on the cell growth inhibition of Doxorubicin at different concentrations.

DRWD [0046] FIG. 26: Influence of nicotinamide on the cell growth inhibition of K 22339 at different concentrations.

DRWD [0047] FIG. 27: Influence of nicotinamide on the cell growth inhibition of K 22387 at different concentrations.

DETD [0069] In a preferred embodiment for compounds according to the invention the "delayed cell death" induced by the compounds can be antagonized by the addition of niacinamide as can be seen in FIGS. 20 to 27, as for Tiazofurin, Selenazofurin, Azaserin, 6-Diazo-5-oxo-L-norleucine, and Doxorubicin no measurable influence of the addition of nicotinamide on the action of these toxic compounds on cell growth is seen, whereas the DCD triggered by for example K22339 and K22387 can be antagonized, as described in the Nicotinamide Reversibility Assay.

DETD [0071]

TABLE 3b

Compound	NAD(P) pmol/10.sup.6 cells	NAD(P) pmol/mg protein	% of Control
Control	531	374.00	100.0
6-Amino-nicotinamide	466.98	329.34	88.0
Tiazofurin	414.47	292.30	78.1
Selenazofurin	372.29	372.29	70.2
Azaserine	530.64	374.23	100.0
6-Diazo-5-oxo-L-norleucine	586.39	413.55	110.5
Doxorubicin	539.74	380.65	101.7

DETD [0514] For the detection of specific inhibitors of niacinamide phosphoribosyltransferase (NAPRT) the assay referred to in the Examples Section as Nicotinamide Reversibility Assay can be used in a preferred embodiment of the invention.

DETD [0527] The .sup.14C-labeled components of the cell extracts were separated and identified using two thin-layer chromatography (TLC) systems. 2 μl of each cell extract was transferred to a cellulose and a poly(ethyleneimine) (PEI) cellulose TLC foil using a DC-Probenautomat

III (CAMAG, Muttenz, Switzerland). The cellulose foils were developed using 1 M NH.sub.4 acetate:ethanol (3:7) as solvent (Pinder, S., Clark, J. B. and Greenbaum, A. L. (1971) The Assay of Intermediates and Enzymes Involved in the Synthesis of the Nicotinamide Nucleotides in Mammalian Tissues. Methods in Enzymology. Academic Press, New York. Vol. XVIIIB pp. 20-46). The PEI cellulose plates were developed with 0.05 M lithium chloride (Barton, R. A., Schulman, A., Jacobson, E. L. and Jacobson, M. K. (1977) Chromatographic Separation of Pyridine and Adenine Nucleotides on Thin Layers of Poly(ethyleneimine) Cellulose. J. Chromatogr. 130: 145-150).

DETD [0539] Nicotinamide Reversibility Assay

DETD [0540] Hep G2 cells derived from a human liver carcinoma were plated at a density of 20,000 cells/ml in 12-well plastic dishes. Cultivation occurred in Richters IMEM-ZO nutrient medium with 5% fetal calf serum (FCS) in a tissue culture incubator with a gas mixture of 5% CO.sub.2 and 95% air at a temperature of 37° C. One day after plating, the culture medium was aspirated from the cells and replaced by fresh medium which contained the respective concentrations of the test compounds and where applicable of the nicotinamide. For the individual concentrations and the controls without test compounds, three-fold batches were done for each. Three days after the beginning of treatment, the medium was again renewed with the test compounds and where applicable the nicotinamide. After six days of compound incubation, the test was ended and the protein amount in the individual wells was determined with the sulforhodamin-B-method (according. to P. Skehan et al.: New Colorimetric Cytotoxicity Assay for Anticancer-Drug Screening. J. Natl. Cancer Inst. 82: 1107-1112, 1990). The IC.sub.50-values were taken from the dose-response curves and given as a comparative measurement for the activity of the test compounds.

DETD [0568] Pinder, S., Clark, J. B. and Greenbaum, A. L. (1971) The Assay of Intermediates and Enzymes Involved in the Synthesis of the Nicotinamide Nucleotides in Mammalian Tissues. Methods in Enzymology. Academic Press, New York. Vol XVIIIB pp. 20-46

DETD [0609] 4. Berger, N. A., Berger, S. J. , Catino, D. M., Petzold, S. J., Robins, R. K. (1985) Modulation of nicotinamide adenine dinucleotide and poly(adenosine diphosphoribose) metabolism by the synthetic "C" nucleoside analogs, tiazofurin and selenazofurin. J. Clin. Invest. 75: 702-709

DETD [0610] 5. Boulton, S., Kyle, S., Durkacz, B. W. (1997) Low nicotinamide mononucleotide adenylyltransferase activity in a tiazofurin-resistant cell line: effects on NAD metabolism and DNA repair. Br. J. Cancer. 76: 845-851

DETD [0612] 7. Barclay, R. K., Phillipps, M. A. (1966) Effects of 6-Diazo-5-oxo-L-norleucine and other tumor inhibitors on the biosynthesis of nicotinamide adenine dinucleotide in mice. Cancer Res. 26: 282-286

IT 200867-83-0 201034-75-5
(vitamin PP compds. as cytoprotective agents in chemotherapy)

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FILE 'MEDLINE, CAPLUS, WPIDS, USPATFULL' ENTERED AT 16:31:20 ON 09 AUG 2007

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L5             0 L3 NOT PY>2000

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L6   ANSWER 1 OF 1  USPATFULL on STN
ACCESSION NUMBER:        2002:239033  USPATFULL  Full-text
TITLE:                   Use of pyridyl alkane, pyridyl alkene and/or pyridyl
                         alkine acid amides in the treatment of tumors or for
                         immunosuppression
INVENTOR(S):             Biedermann, Elfi, Vaterstetten, GERMANY, FEDERAL
                         REPUBLIC OF
                         Hasmann, Max, Neuried, GERMANY, FEDERAL REPUBLIC OF
                         Loser, Roland, Feldafing, GERMANY, FEDERAL REPUBLIC OF
                         Rattel, Benno, Munich, GERMANY, FEDERAL REPUBLIC OF
                         Reiter, Friedemann, Putzbrunn, GERMANY, FEDERAL
                         REPUBLIC OF
                         Schein, Barbara, Neufahrn, GERMANY, FEDERAL REPUBLIC OF
                         Seibel, Klaus, Grafelfing, GERMANY, FEDERAL REPUBLIC OF
                         Vogt, Klaus, Munich, GERMANY, FEDERAL REPUBLIC OF
PATENT ASSIGNEE(S):      Klinge Pharma GmbH, Munich, GERMANY, FEDERAL REPUBLIC
                         OF (non-U.S. corporation)

                              NUMBER        KIND    DATE
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PATENT INFORMATION:      US 6451816          B1   20020917
APPLICATION INFO.:       US 1998-216482           19981218  (9)
RELATED APPLN. INFO.:    Continuation of Ser. No. WO 1997-EP3244, filed on 20
                         Jun 1997
DOCUMENT TYPE:           Utility
FILE SEGMENT:            GRANTED
PRIMARY EXAMINER:        Rotman, Alan L.
ASSISTANT EXAMINER:      Desai, Rita
LEGAL REPRESENTATIVE:    Fitch, Even, Tabin, & Flannery
NUMBER OF CLAIMS:        18
EXEMPLARY CLAIM:         1
NUMBER OF DRAWINGS:      0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT:              4285
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB       The invention relates to the use of pharmacologically valuable pyridyl
         alkane, pyridyl alkene and/or pyridyl alkine acid amides according to
         general formula (I) in the treatment of tumors or for immunosuppression.
         ##STR1##


CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT  201034-75-5P
        (preparation of pyridine derivs. as antitumor agents and
immunosuppressants)
RN   201034-75-5  USPATFULL
CN   2-Propenamide, N-[4-(1-benzoyl-4-piperidinyl)butyl]-3-(3-pyridinyl)- (9CI)
         (CA INDEX NAME)
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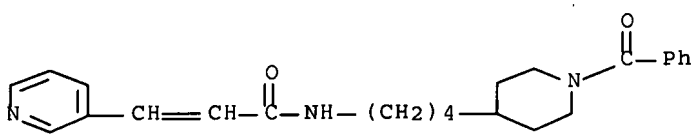

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L2              2 S L1 EXA FULL

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     2007
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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
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